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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/785,951	02/16/2001	Michael John Mullan	01097.0008U2	7348

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EXAMINER	
CROUCH, DEBORAH	
ART UNIT	**PAPER NUMBER**
1632	

DATE MAILED: 12/15/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/785,951	MULLAN, MICHAEL JOHN	
	Examiner	Art Unit	
	Deborah Crouch, Ph.D.	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on *15 September 2003*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *21-32* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☒ Claim(s) *25-28, 31 and 32* is/are allowed.

6)☒ Claim(s) *21-24,29 and 30* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *16 February 2001* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. §§ 119 and 120

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

13)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

a) ☐ The translation of the foreign language provisional application has been received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____.
4) ☐ Interview Summary (PTO-413) Paper No(s). _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on September 15, 2003 has been entered. Claims 21-32 are pending.

The rejection of claims 25-28 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 11 and 12 of U.S. Patent No. 5,455,169 has been over come by filing a proper terminal disclaimer. The terminal disclaimer filed on September 15, 2003 disclaiming the terminal portion of any patent granted on this application that would extend beyond the expiration date of 5,455,169 has been reviewed and is accepted. The terminal disclaimer has been recorded.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 21-24, 29 and 30 remain rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention for reasons presented in the office action mailed March 10, 2003.

Claims 21-24, 29 and 30 are drawn to non-human transgenic animals comprising in a germ or somatic cells a nucleic acid encoding human amyloid precursor protein including the nucleotides encoding codon 670 and 671 of human amyloid precursor protein isoforms, operably linked to a promoter, wherein the amino acid encodes at amino acid 670 other than lysine and/or at amino acid 671 other than methionine, and wherein the animal

expresses the human amyloid precursor protein or fragment thereof which encodes an amino acid other than lysine at codon 670 and/or an amino acid other than methionine at codon 671, and wherein the animal comprises a nucleic acid that further encodes other than valine at amino acid 717, wherein in the animal is useful for the study of the biochemistry of APP and β-amyloid metabolism, and methods of screening agents capable of treating Alzheimer's disease comprising contacting an agent with the transgenic non-human animal and monitoring the expression, processing or deposition of amyloid precursor protein or fragments thereof.

Applicant argues that the examiner has instituted an arbitrary standard for enablement. Applicant argues that the specification discloses several credible uses for the claimed transgenic animal other than the examiner's stated use as a disease model. Applicant argues that the office has elevated a preferred feature of animal model to the status of inoperability. Applicant argues that a product only requires one enabled use to meet the standards of 35 U.S.C. 112, first paragraph. Applicant states that the specification discloses that the animal can be used for screening drugs and evaluating drug effectiveness, and as a tool for defining the biochemistry of APP and β-amyloid metabolism. Applicant argues that these do not require the specific pathogenesis defined by the patent office. Applicant states that is an error for the office to presume that a particular stage of pathogenesis be required.

Applicant should review the claims of record, where they will see that claim 22 required that the animal have a neuropathological characteristic of Alzheimer's disease. Applicant made the requirement that the animal have the characteristic, and, as applicant pointed out, the animal is disclosed as a model for determining drug efficacy. To so determine it is readily apparent the animal would need to have some "characteristic" of Alzheimer's Diseases. The office made no error. The error is that the specification failed to

provide any reasonable prediction of an Alzheimer's disease characteristic associated with the claimed animal. Alzheimer's disease has a broad range of characteristics. The specification fails to point to any and the examiner could not find that even expression of APP was contemplated.

Applicant argues that an animal model is comprised of any condition found in an animal that is of value in studying a biological phenomenon. Applicant argues that it sufficient that the animal translate expressed APP mutant RNA because the expression of mutant RNA is sufficient for studying a biological phenomenon of APP expression. Applicant argues that it is an error to require that for each and every utility to which the claimed transgenic animals can be applied must relate to full-blown or specific Alzheimer's pathology. These arguments are not persuasive.

It is noteworthy that applicant cannot point to a location in the specification that states that expression of mutant mRNA or translation of the mutant mRNA is an Alzheimer's disease characteristic that will be seen in the claimed animals, or that these characteristics are useful assay points. The fact is that the specification does not so disclosed. It is true the specification states the transgenic animals can be used "as model systems for screening for drugs and evaluating drug effectiveness. Additionally, such model systems provide a tool for defining the underlying biochemistry of APF and β-amyloid metabolism, which thereby provides a basis for rational drug design." However, the specification does not teach what will be assayed to determine drug effectiveness or to define the underlying biochemistry. In particular, examiner could not find any disclosure for expression of the mutant APP to be an assayable Alzheimer's disease characteristic in either determining drug efficacy or in determining the underlying biochemistry of Alzheimer's disease. Thus, there is no guidance from the specification as to which Alzheimer's diseases characteristic, full-blown or otherwise, that the artisan could expect the animal to have so that the animal can be use in

any type of assay. While these utilities or uses of the animal may rise to meet the requirements of 35 U.S.C. 101, they do not rise to the requirements of enablement as the artisan would not know, from the specification, how to use the animals in these utilities. In other words, the specification does not define any condition found in the animals that is of value in studying a biological phenomenon. Thus, there is no enablement of the claimed animals as a disease model. The examiner is not requiring a particular pathology. The examiner is pointing out that the specification fails to correlate any Alzheimer's disease characteristic with the claimed mice. Further, applicant has not pointed to any suggestion in the specification or the art that expression of a mutant APP mRNA or protein is a pathological characteristic of Alzheimer's disease. Amyloid deposition is the crucial pathology of Alzheimer's disease (Hardy, page 838, col. 3, parag. 2, lines 1-5).

Applicant argues that the art teaches that over expression is crucial feature to produce an Alzheimer's disease model. Applicant has argued that Pierrat et al (response pages 9-10) teaches the development of plaques in mice expressing a DNA sequence encoding APP 670/671 (KM>NL) operatively linked to either the mouse or human Thy-1 promoter. Applicant continues to argue that in two other mice known in the art to develop, Hsiao et al and Games et al, constructs were used that resulted in the over expression of the mutant APP. From this applicant concludes that the general opinion of those skilled in the art is over expression is responsible for plaque formation not the particular promoter used. This argument is not persuasive.

Over expression is a direct result of promoter activity. Deposition of mutant amyloid protein and/or plaque formation might be due to the mutant APP. There is no evidence that the over expression achieved by Pierrat et al, Hsiao et al and Games et al is not related to the promoter being used.

Applicant argues that the 670/671 mutations produce increased levels of plaque forming β-amyloid than nonmutant APP sequences. Applicant argues that Citron teaches the 695 isoform of the 670/671 mutations produces 6-8 fold more β-APP than with similar expression levels of using nonmutant forms of the protein. Applicant argues that this phenotype confirms that the animal disclosed can be used to study the underlying biochemistry of APP or β-amyloid metabolism. Applicant argues that use of the claimed mutation facilitates the development of neuropathological β-amyloid plaques at lower expression levels of APP. Applicant states the patent office is not justified in asserting that the only recognized utility requires an Alzheimer's specific neuropathology.

Citron states that the 670/671 mutation results in 6-8 fold more A/β not 6-8 fold more β-APP. Citron is stating that the mutation result in 6-8 fold more of the 39-43 amino acid A/β found in amyloid plaques. The expression Citron refers to is not expression of the full-length protein but to production of the fragment of the full-length protein found in plaques. However, this evidence of Citron does not alter the fact that the specification fails to disclosure a characteristic of the claimed animals that makes it useful for determining drug effectiveness in treating Alzheimer's disease or to study the biochemistry of APP or β-amyloid metabolism. Given the present disclosure, the artisan would not know what characteristic to assay; Alzheimer's specific or otherwise. If applicant is saying that mere expression of the mutant APP mRNA or mutant APP is the point of assay, the specification does not so state in any area of the disclosure related to using the animal. There needs to a clear contemplation in the specification as to how the animal is to be used and enablement of that use. Without describing the effect of expression or of over expression of the 670/671 APP mutant protein, the use, even if disclosed, is not enabled.

Applicant argues that "pathogenesis" means "the development of a diseased or morbid condition." Applicant argues that it is well understood that the initial biochemical

steps that lead to the manifestation of disease constitute a part of the development of the disease. Applicant argues that one of skill in the art would have realized a use of the claimed animals to study the development of Alzheimer's disease. These arguments are not persuasive.

Neither the specification nor the art are clear on the issue of the development of Alzheimer's disease. There is no evidence of record that the artisan at the time of filing would have recognized the claimed animals as useful for studying the development of Alzheimer's disease because there is no evidence of record that the artisan at the time of filing would have recognized mutant APP expression alone as a pathogenesis of Alzheimer's disease. As stated above Hardy et al do not state such.

Applicant argues that the art at the time of filing taught that the development of plaques or abnormal aggregates of β-amyloid in the brain of a subject is the first step in the pathogenesis of Alzheimer's disease. Applicant argues the specification teaches several enabled uses for the claimed animal in this regard. Applicant argues that the animals could be used to assay for agents that inhibit, prevent or reverse the progression of Alzheimer's disease. These arguments are not persuasive.

The specification discloses the production of transgenic nonhuman animals expressing APP 670/671, and that these animals can be used to study APP or β-amyloid biochemistry/metabolism, and assays for determining drugs or agents that inhibit, prevent or reverse the progression of Alzheimer's Disease. However, the specification never discusses what is to be observed in the animals that correlate to APP or β-amyloid biochemistry, metabolism or inhibition, prevention or reversal of Alzheimer's disease progression. The deficiency in the disclosure is in disclosing exactly what phenotype does the artisan monitor in any of these uses of the animals. Without such a disclosure, the artisan would not know how the implement the uses of the animals, which it the same as

not being to use the animals. It is responsibility of the disclosure to teach the artisan how to use the animals and not for the artisan to decide how to use the animals. A general disclosure of a use without a mention of the phenotype or characteristic monitored in the uses does not teach how to the use the claimed animals.

Applicant argues that issuance of US Patent 5,720,936 is factually similar to the present case, and that in this patent office recognized that the mice had a use in screening compounds that can affect the amount of APP and β-amyloid peptide production. Applicant argues that the office has recognized that a transgenic animal can be used to study APP processing in the pathogenesis of AD without recapitulating the pathological cascade. These arguments are not persuasive.

As applicant is aware, each application is examined on its own merits. The specification of '936 may offer more guidance as to what to monitor in using the mice as an assay system, there may be declarations present that were persuasive or other evidence. However, the issuance of '936 does not relieve the present specification from needing to disclose how to use the animals and enable that use.

Applicant argues that at the time of filing that the art also taught that the NSE promoter could be used to express APPswe. Applicant argues that a disclosure of the prion promoter in the present invention is not necessary. Applicant argues that in Malherbe, cited in the previous office action, the problem wasn't the promoter but that the experiment wasn't designed properly because the mouse wasn't examined after one year. Applicant then argues that Malherbe at most shows that the NSE construct takes longer than one year to manifests deposits. These arguments are not persuasive.

Applicant is arguing knowledge not of record. Applicant should file a declaration of their knowledge that the Malherbe mice exhibited deposits after one year. However, the issue here isn't whether there were or weren't deposits in applicant's mice, but whether or

not applicant has taught how to use the animals claimed. At no place does the specification contemplates the expression of APP 670/671 would lead to plaques. Further the present specification never discloses what to assay for or what to study.

Applicant argues that the skilled artisan would know the proper site of transgenic integration through routine experimentation. Applicant argues that the art regarding transgenic animals in general and Swedish mutation mice specifically showed that the problems suggested could be overcome. Applicant cites Pierrat et al and Quon et al. This argument is not persuasive.

Pierrat et al and Quon et al are not applicable as they only disclose transgenic mice expressing an APP and no other animal. Further, in transgenesis, there is no means to determine a particular site for insertion of the APP DNA sequence. Applicant's animals were made by fertilized ova microinjection, which does not permit one to determine a proper site of integration.

Applicant argues that Lannfelt states that the problem with determining the effect of expressing a mutant APP in mice that these studies are governed by commercial organization. Applicant argues that Lannfelt states that the mutant APP may lead to a useful animal. Applicant argues that Lannfelt states the deposition of β-amyloid in the brain is a diagnostic hallmark of Alzheimer's disease. Applicant argues that an animal having the hallmark of AD has a use in the study of the hallmark and its development. These arguments are not persuasive.

There is no evidence that applicant contemplated the hallmark of β-amyloid deposition. The examiner would agree that deposition is a laudable hallmark of Alzheimer's disease, but applicant never disclosed their mice developing such a feature. If applicant did so contemplate, then applicant should amend the claims to reflect such. Further, regardless of why reports of mice expressing mutant APP isoforms were absent at the time of filing,

does not alleviate the present specification from having to teach how to make non-mouse animals expressing APP. While Lannfelt may be believed such mice would be more useful in the study of Alzheimer's disease or in developing Alzheimer's disease therapies does not enable the production of non-mouse animals.

Applicant argues that enablement only requires that the skilled artisan to extrapolate the disclosed or known results to the claimed invention. Applicant argues that Higgins teaches that mice can express the human APP 695 gene and produce β-amyloid protein. Applicant argues that the mice of Higgins did develop neuropathology of Alzheimer's disease and names neuropil threads and neurofibrillary tangles detected by monoclonal antibody. Applicant argues that the patent office continues to allege that mice as a species are resistant to expressing a mutant APP gene. Applicant argues that the office is rejection their argument that Hsiao shows mice expressing APP695 have AD pathologies. Applicant argues that the examiner is wrong that the promoter used by Malherbe and Hsiao had anything to do with the outcomes in those cases. Malherbe expressed APP695swe from an NSE promoter and did not develop β-amyloid deposits and that Hsiao expressed the same DNA sequence from the prion promoter and did obtain Alzheimer's disease pathologies. Applicant states that the examiner did not back up this analysis with scientific reasoning. Applicant argues that they have overcome the differences between Malherbe and Higgins by showing that overall expression level is responsible for plaque formation. These arguments are not persuasive.

If Malherbe and Hsiao expressed the same mutant APP but using the NSE and prion promoters, respectively, and that expression resulted in either no deposition or the formation of Alzheimer's disease pathologies, then that should be pretty obvious that the promoter used in crucial in developing a pathology. In fact, over expression of any gene is a function of the promoter. Perhaps applicant is confusing over expression of the APP DNA

sequence with the mutant APP over producing amyloid deposition when compared to wild type APP. However, Malherbe and Hsiao clearly indicate that for expression of the gene, that is the production of APP, and the development of Alzheimer's disease pathologies is related to the promoter. However, this is not even the issue presently. Applicant is trying to argues that the claimed animals have a use enabled by the specification, but they do not demonstrate or assert that the specification actually discloses a phenotype to the animals that can be used with any of the argued uses. The specification must disclose and enable the use, and not the art.

With regards to the report in Felsenstein that rats failed to demonstrate APP expression does not mean that the claimed invention is not enabled. Applicant argues that the rats were analyzed at a young age and does not reflect what would have happened if the experiment had been carried for a longer period of time. This argument is not persuasive.

Applicant is claiming nonhuman transgenic animals, but has exemplified mice. Felsenstein teaches that rats do not express APP. Applicant teaches nothing about other animals. Thus, the negative teaching by Felsenstein is sufficient to indicate that applicant's breath is not enabled. The remainder of applicant's argument is speculation. If applicant has evidence that the rats later expressed APP or developed a pathology related to Alzheimer's disease, that evidence should be filed in a 132 declaration.

Applicant argues that Quon teaches the production of transgenic mice expressing APP751 from an NSE promoter. Applicant argues that this mouse was known at the time of filing as a model for the study of the pathogenesis or development of Alzheimer's disease. This argument is not persuasive.

While Quon and US Patent 5,387,742 teach the production of mice having amyloid deposits where the mice express wild type APP751 under the control of the NSE promoter,

this does not provided evidence that the presently claimed animal would develop the same phenotype. As demonstrated Malherbe expressed an APP 670/671 mutation from the NSE promoter and did not achieve effective expression. Applicant's exact example was published as failed. Further each of these references is to mice. In addition, the patents to Hsiao, Wadsworth and Cordell are all limited to mice. Thus applicant cannot rely on these patents as evidence that transgenic animals were enabled at the time of filing.

Applicant's arguments frequently are not consistent. Some places applicant argues that only expression is required. However, there is nothing of record or in the specification that production of either an APP mRNA or an APP is a phenotype the art regards as relevant to assay for either Alzheimer's disease treatment or APP metabolism. Then applicant argues that the art teaches mice expressing various APP constructs and the animals develop a hallmark of Alzheimer's. This is true for applicant's specific example of the Thy-1 promoter, while not for the exemplified NSE promoter. However, the issue with a Thy-1 mouse or animal, is that there is nothing in the specification that states what phenotype or characteristic of the claimed transgenic animals is to assayed to determine either drug efficacy or APP metabolism. There is nothing in the art that mRNA or protein production is determining phenotypes for determining drug efficacy. The specification provides no details on what is meant by APP metabolism. Thus, the disclosed uses of the animal are not enabled because the artisan at the time of filing would not know what to assay or what to analyze.

Claims 25-28, 31 and 32 are allowable.

Claims 21-32 remain free of the prior art for reasons of record.

All claims are drawn to the same invention claimed in the application prior to the entry of the submission under 37 CFR 1.114 and could have been finally rejected on the

grounds and art of record in the next Office action if they had been entered in the application prior to entry under 37 CFR 1.114. Accordingly, **THIS ACTION IS MADE FINAL** even though it is a first action after the filing of a request for continued examination and the submission under 37 CFR 1.114. See MPEP § 706.07(b). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Deborah Reynolds, SPE of AU 1632 whose telephone number 703-305-4051. The examiner can normally be reached on M-Th.

Should inquiries be made on or after January 12, 2004, the examiner's phone number will be 571-272-0727. Deborah Reynolds will be reached at 571-272-0734.

The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306 for regular and After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0916.

Deborah Crouch

Deborah Crouch, Ph.D.
Primary Examiner
Art Unit 1632